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INHALATION TOXICITY OF GF VAPOR IN RATS AS A FUNCTION OF EXPOSURE CONCENTRATION AND DURATION AND ITS POTENCY COMPARISON TO GB

J. Steven Anthony
Mark V. Haley
James H. Manthei
Ruth A. Way
Dave C. Burnett
Bernardita P. Gaviola
Douglas R. Sommerville
Ronald B. Crosier
Robert J. Mioduszewski
Sandra A. Thomson

RESEARCH AND TECHNOLOGY DIRECTORATE

Charles L. Crouse
Kathy L. Matson

GEO-CENTERS, INC.
Abingdon, MD 21009

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Aberdeen Proving Ground, MD 21010-5424

DEPARTMENT OF THE ARMY
U.S. Army Edgewood Chemical Biological Center
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Sandra J. Johnson
SANDRA J. JOHNSON
Chief, Technical Releases Office

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Anthony, J. Steven; Haley, Mark V.; Manthei, James H.; Way, Ruth A.; Burnett, Dave C.; Gaviola, Bernardita P.; Sommerville, Douglas R.; Crosier, Ronald B.; Mioduszewski, Robert J.; Thomson, Sandra A. (ECBC); Crouse, Charles L.; and Matson, Kathy L. (GEO-CENTERS, Inc.)

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The inhalation toxicity of cyclohexyl methylphosphonofluoridate (GF) was examined in male and female Sprague-Dawley rats exposed by whole-body in a dynamic 750-L chamber. The objectives of this study were to 1) validate vapor detection methods for GF, starting in the lethal to near-lethal concentration range; 2) examine dose-response effects of inhaled GF vapor, analyze the relationship between concentration (C) and exposure duration (t) in determining probability of lethality; and 3) establish a lethal potency ratio between GF and the more volatile agent sarin (GB). The GF vapor concentrations were generated for exposure times of 10, 60, and 240 min. Dose-response curves with associated slopes were determined by the Bliss probit method. Concentration-exposure time values for lethality in 50% of the exposed population (LCt_{50}) were calculated for 24-hr and 14-day post exposure periods for 10-, 60-, and 240-min exposures. At longer exposure durations, the LCt_{50} for GF was less than for GB, but at shorter exposure durations, the LCt_{50} for GF was more than for GB. Empirical models, consisting of the toxic load model plus higher order terms, were fit to the data to test the adequacy of the model and to identify statistically significant patterns.

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PREFACE

The work described in this report was authorized under Project No. 206023. This work was started in January 2001 and completed in January 2002. The experimental data are contained in laboratory notebooks 01-0006 and 01-0081. Raw data and the final report from this study are stored in the Toxicology Archives, Building E3150, Aberdeen Proving Ground, MD.

In conducting this study, investigators adhered to the "Guide for the Care and Use of Laboratory Animals," National Institutes of Health Publication No. 86-23, 1985, as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, Commission of Life Sciences, National Research Council, Washington, D.C. These investigations were also performed in accordance with the requirements of AR 70-18, "Laboratory Animals, Procurement, Transportation, Use, Care, and Public Affairs," and the U.S. Army Edgewood Chemical and Biological Center (ECBC) Institutional Animal Care and Use Committee (IACUC), which oversees the use of laboratory animals. This project's assigned IACUC Protocol No. 01-333, was approved on 2 April 2001.

All animals were cared for as stated in this research protocol and as specified in the NIH Publication No. 85-23, 1985 (or updates). Records were maintained in official ECBC Notebooks in the Life Sciences Official Archives (Bldg. E3150) and/or in the Technical Library (Bldg. E3330). Studies were conducted under, and in compliance with, current GLP standards and they were reviewed periodically by the QA Coordinator or his designee.

The performance of this study was consistent with the objectives and standards in "Good Laboratory Practices for Non-clinical Laboratory Studies" (21 CFR 58, Food and Drug Administration, U.S. Department of Health and Human Services, April 1988).

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QUALITY ASSURANCE

This study, conducted under Protocol 01-333, was examined for compliance with Good Laboratory Practices as published by the U. S. Environmental Protection Agency in 40 CFR Part 792 (effective 17 Aug 1989). The date of this inspection and the dates the results were reported to the Study Director and management were as follows:

Phase Inspected	Date	Date Reported
Inhalation exposure	18 Apr 01	19 Apr 01
Data and Final Report	1 May 03	1 May 03

To the best of my knowledge, the methods described were the methods followed during the study. The report was determined to be an accurate reflection of the raw data obtained.

DENNIS W. JOHNSON
Quality Assurance Coordinator
Toxicology, Aerosol Sciences and
Obscurants Senior Team
Research and Technology Directorate

CONTENTS

1. INTRODUCTION 9

2. MATERIALS AND METHODS 10

2.1 Chemicals 10
2.2 Vapor Generation 10
2.3 Sampling and Monitoring Exposure Chamber GF Vapor 10
2.3.1 Thermal Desorption Solid Sorbent Tube 11
2.3.2 Phosphorus Monitor (HYFED) 11
2.4 Animal Exposures 11
2.4.1 Animal Model 11
2.4.2 Whole-Body Inhalation Exposures 12
2.4.3 Observation of Clinical Signs 12
2.5 Data Analysis 12

3. RESULTS 13

3.1 Lethal Responses 13
3.2 Pupil Diameter 13

4. DISCUSSION 13

4.1 Literature Overview of GF Inhalation Exposures 13
4.2 Formulating an Empirical Lethality Probability Model for the Rat 14
4.3 LCt_{50} Curves from Empirical Lethality Probability Model 15
4.4 Formulating a Lethal Probability Model for Operational Applications (Toxic Load) 15
4.5 Male vs. Female Sensitivity to GF Vapor-Induced Lethality 15
4.6 Pupil Response to GF Vapor Exposure 16
4.7 Potency Ratio 16

5. CONCLUSIONS 16

LITERATURE CITED 33

APPENDIXES

A - PROBIT ANALYSES A-1

B - PROBIT-TYPE BINARY LOGISTIC REGRESSION ANALYSES FOR EFFECTS OF SEX, CONCENTRATION, AND AGENT ON LETHAL RESPONSE TO VAPOR EXPOSURE B-1

FIGURES

1. Structures of GB and GF 17

2. Schematic of Inhalation Exposure Chamber and Vapor Generation System 17

3. Experimental Exposure Chamber System 18

4. Effects of GF Vapor Exposure on Pupil Diameter 19

5. Pupil Diameter vs. GF Vapor Exposure Duration 19

6. Lethality Within 24-hr From GF Vapor 20

7. Lethality Within 14 Days From GF Vapor 20

8. LCt_{50} vs. GF Vapor Exposure Duration for Male and Female Rats 24-hr Post-Exposure – same toxic load exponent (n) 21

9. LCt_{50} vs. GF Vapor Exposure Duration for Male and Female Rats 24-hr Post-Exposure – different toxic load exponent (n) 21

TABLES

1. Agent Vapor Pressure Comparisons 22

2a. Summary of GF Vapor-Induced Lethality in Male Rats 22

2b. Summary of GB Vapor-Induced Lethality in Male Rats 23

3a. Summary of GF Vapor-Induced Lethality in Female Rats 23

3b. Summary of GB Vapor-Induced Lethality in Female Rats 24

4. Summary of GF Vapor-Induced Sub-Lethal Effects in Male Rats 24

5. Summary of GF Vapor-Induced Sub-Lethal Effects in Female Rats 25

6. LC_{50}, LCt_{50}, Slopes and Fiducial Limits for GF and GB Vapor-Induced Lethality (24-hr post exposure) at 10, 60, and 240 min 25

7. LC_{50}, LCt_{50}, Slopes and Fiducial Limits for GF and GB Vapor-Induced Lethality (14 day post exposure) at 10, 60, and 240 min 26

8. Analysis of Variance of Rat Pupil Diameters for Rats with a Complete Set of Six Pupil Measurements Model: Pupil Diameter versus Observation Time and Rat 27

9. Mean Pupil Diameters and Standard Errors for Surviving Rats Having a Complete Set of Six Pupil Measurements 30

10. Historical Overview of GF Inhalation Exposures 30

11a. Relative Potency for GB vs. GF – 24-hr data 31

11b. Relative Potency for GB vs. GF – 14-day data 31

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INHALATION TOXICITY OF GF VAPOR IN RATS AS A FUNCTION OF EXPOSURE CONCENTRATION AND DURATION AND ITS POTENCY COMPARISON TO GB

1. INTRODUCTION

Critical toxicological data gaps need to be filled in order to address issues concerning potential low-level chemical warfare agent (CWA) exposure on the battlefield. Filling data gaps for exposure to airborne chemical warfare agents is essential for predicting performance degradation of personnel, enhancing risk assessment modeling tools and defining detection thresholds which are physiologically relevant. Toxicological data (low level exposures) serve as the basis for decisions regarding health hazard analyses, setting requirements for materiel developers, and decontamination issues i.e., how dirty is clean enough. Data are provided for detector development (e.g., how low detectors need to go) required protective posture guidelines (e.g., when is it "safe" to come out of protective posture), and decontamination (e.g., how "dirty" is clean enough following decontamination).

Traditional predictions of sarin (GB) dosage-mortality relationships over time using Haber's rule[1] have not been supported by the results of experimental studies involving exposure durations up to six hours.[2-3] An inverse linear relationship between concentration (C) and time (t), as implied by Haber's Law, does not exist in these situations. Mioduszewski *et al.*, (2001) examined the dose-response effects of sarin (GB) vapor for lethality in rats at various exposure durations up to six hours. It was found that the assumption regarding the relationship between exposure dose and lethality used historically (Haber's rule; Haber, 1924) to predict CW agent toxicity was not adequate to describe the lethal response data over time. For many acutely toxic gases and aerosols, toxic effects cannot be adequately related to the Ct product.[4-5] For these materials, the influence of concentration is usually more pronounced than that of exposure time. In other words, a high concentration for a short period has a more severe effect than a low concentration for a longer time, given the same Ct.

The paucity of cyclosarin (GF) inhalation toxicity data in the literature may be due to the inherent problems associated with the generation of less volatile agents.[6-8] Table 1 compares the vapor pressures of GF, GB, mustard (HD) and the nerve agent VX.[9] Structures of GB and GF are shown in Figure 1. GF is nearly 50x less volatile than GB and 2x less volatile than the blistering agent HD. For vapor exposure experiments involving GF, conditions must be monitored to assure complete vapor generation (and avoid aerosol generation) due to GF's lower vapor pressure. No published references were found in which multiple concentrations and exposure times exceeding 10 min were examined in a single study.[10-13] The objectives of the present study were to 1) validate vapor detection methods for GF starting in the lethal to near-lethal concentration range and continuing to low-level concentrations; 2) examine the relationship between concentration (C) and exposure duration (t) with the probability of lethality in rats exposed to GF vapor; and 3) establish the lethality potency ratio between GF and GB.

2. MATERIALS AND METHODS

2.1 Chemicals.

Cyclohexyl methylphosphonofluoridate (Cyclosarin, GF) or Isopropyl methylphosphonofluoridate (Sarin, GB) was used in all vapor exposures throughout the study. According to an established method, seven ^{31}P NMR analyses were performed for each agent to certify the purity of the test materials.[14] GF was established as 98.9 ± 0.5 wt % pure, and GB was 99.1 ± 0.5 wt % pure. No impurity peaks were detected in the phosphorus spectra. A high purity grade of triethylphosphate (>99.9% TEP; Aldrich Cat. No. 24,089-3) was used as the internal standard for the GF and GB purity assays. External standards were prepared using high purity grade hexane solvent (purity> 87.7% n-hexane, >99.9% n-hexane and isomers; Supplier: Burdick and Jackson).

2.2 Vapor Generation.

The vapor generation system was located at the chamber inlet and was contained within a stainless steel glove box maintained under negative pressure (Figure 2). A gas-tight syringe, containing the test material, was secured into a variable rate, pulse-free syringe drive with the material delivered into a spray atomizer. A syringe needle (stainless steel, 26 gauge, 3" length) was used in the spray atomizer for all GF and GB exposures. For generation of GB a 25-gauge needle had previously been used[2-3], but initial experiments determined the need to break the less volatile GF liquid into droplets of smaller diameters. Liquid GF or GB entered the top of the sprayer, and mixed with compressed air (30 psi) at 12 L/min. The compressed air broke the liquid into fine droplets and facilitated vapor formation.

Concentration uniformity was checked at several locations throughout the chamber, including areas directly above the animal cages and inside the animal cages. At higher generated agent concentrations, vacuum pumps drew air through glass fiber filter pads at high flow rates to assure the absence of aerosols. Subsequent analyses showed that no agent aerosol was present.

2.3 Sampling and Monitoring Exposure Chamber GF Vapor.

The 750-L dynamic whole-body exposure chamber was located in the middle of a 20,000-L containment chamber (Figure 3). The exposure chamber was hexagonal and constructed of stainless steel. Plexiglas windows that ran the length of each side permitted observation of toxic signs in the rats during exposure runs. The interior of the exposure chamber was maintained under negative pressure as recorded by a calibrated magnahelix (0-1" water). Room air was drawn through the exposure chamber (400-1700 L/min) and measured at the chamber outlet with a calibrated thermo-anemometer. The rotation speed of the exposure chamber fan [in revolutions per min (rpm)] was also monitored as a check for airflow readings. Temperature and humidity were recorded for every exposure.

2.3.1 Thermal Desorption Solid Sorbent Tube.

The thermal desorption solid sorbent tube system consisted of a heated transfer line, heated external switching valve, thermal desorption unit, and a gas chromatograph with flame ionization detection. Samples were drawn from the middle of the exposure chamber through a six-foot silica transfer line (1/16" o.d. x 0.004" i.d.) and held at 150 °C. Flow rates (measured before and after sampling) were either 20 ml/min or 40 ml/min, and sampling times were either 1, 4, or 5 min, depending on chamber concentration. The sample entered a heated six-port gas-switching valve before depositing onto a Tenax-TA sorbent tube. The solid sorbent material was used to trap the vapor, concentrate it, and inject it directly onto a gas chromatograph-flame ionization detector (GC-FID) for subsequent detection and quantitation. External standards were injected into the end of the transfer line to simulate identical collection conditions between standards and samples. Separate calibration curves for each agent were used to calculate chamber concentrations. To increase the accuracy of experimental concentrations, samples were continually drawn during the exposures as often as the experimental sampling cycle would allow.

2.3.2 Phosphorus Monitor (HYFED).

Real-time monitoring of chamber concentration was performed with a phosphorus analyzer (HYFED, Model PH262, Columbia Scientific, Austin, TX). Output of the analyzer was recorded on a dual channel strip chart recorder depicting the concentration profile (rise, equilibrium, and decay) of the chamber along with stability of concentration during the exposure time. The rise in concentration, or chamber equilibration time, is dependent on various conditions with airflow through the chamber being the most dominant. Chamber sampling was only performed during the chamber equilibrium phase. Following the 10-min purge time, both the HYFED response and recorder output returned to baseline, indicating that the chamber was sufficiently purged.

2.4 Animal Exposures.

2.4.1 Animal Model.

Young adult male and female Sprague-Dawley rats (8-10 weeks, specific pathogen-free) were obtained from Charles River Laboratories, Inc., Wilmington, MA. The animals were identified by tattoo on the tail, segregated according to sex and housed individually in plastic shoebox cages. They were placed on racks in an American Association for Accreditation of Laboratory Animal Care (AAALAC) accredited facility (Bldg. E-3150). The animals were housed for a minimum of 3 days of quarantine and for the post-exposure period (14 days). Ambient conditions were maintained at 70 ± 5° F, 30 - 70% relative humidity (RH), and a 12:12 hr light-dark cycle. Rats were provided with certified laboratory rat chow and filtered house water *ad libitum*, except during exposure.

2.4.2 Whole-Body Inhalation Exposures.

Prior to exposure, animals were placed in two compartmentalized cages (20" x 14" x 4"), each able to hold 10 rats. All rats served as their own controls. As in Mioduszewski, *et al.* (2001) and (2002), same gender rats were arranged on alternating diagonals within the two cages. Rats were exposed (whole-body) to a fixed concentration of GF or GB vapor for one of three exposure durations (10, 60 or 240 min). During chamber operations, the airflow through the chamber was kept constant. The concentration-time profile generated with this type of chamber is described in a review by MacFarland (1987).[15] His definition of exposure duration was the one used in this study: the interval from the start of the flow of agent into the chamber to the time-point when the agent supply is stopped. Following exposure, the chamber was purged with air for 10 min, and the animals were removed from the chamber.

Due to differences in sensitivity to GF between genders, it was not always desirable to expose both sexes simultaneously to a particular concentration. Certain concentrations might result in an all or none outcome for one gender. Therefore, the sexes were occasionally exposed to different concentrations for a given exposure duration.

2.4.3 Observation of Clinical Signs.

Lethality and sub-lethal clinical signs (e.g., miosis, convulsions, tremors, salivation, prostration, and labored breathing) were monitored (from an observation point outside of the exposure chamber) during and after exposure (within the first hour post-exposure and once daily for up to 14 days). The effects of vapor exposure on pupil size (diameter) were assessed using a simple microscope (Bausch & Lomb, 20x) with a reticule eyepiece insert (Lennox, 1969). Pupil size was measured by counting the number of reticule lines covering the pupil diameter (20 lines/mm or 0.05 mm between lines). Pupil diameters were measured while holding the rat under the microscope under a 200 foot-candle light source as monitored by a light meter (Davis, Model 401025, Extech Instruments, Waltham, MA). Pupil sizes were monitored at least 24 hr prior to exposure, at 1-2 hr following exposure, and at 1, 2, 3, 7, and 14 days post exposure.

2.5 Data Analysis.

A statistical analysis package, version 13 of MINITAB® (Minitab, Inc., State College, PA), was used to analyze the data. MINITAB® has two routines that perform probit-type analyses.[16] The probit analysis routine in the reliability/survival section calculates maximum likelihood estimates of the model coefficients using a modified Newton-Raphson algorithm. The binary logistic regression routine in the regression section also calculates maximum likelihood estimates of the model coefficients, but by an iterative-reweighted least squares algorithm. Because both routines calculate maximum likelihood estimates, they will generally give the same values for the model coefficients. However, the two routines use different approximations of the variance-covariance matrix of the parameters, so the standard errors of the coefficients may differ slightly between the two routines. The probit analysis routine[16] was used for the probit analyses in Appendix A; all other probit-type analyses were

done with the binary logistic regression routine (Appendix B). The binary logistic regression routine is a generalized linear model routine, which equates a link function to a linear model. Selecting normit as the link function results in a probit-type analysis.

3. RESULTS

3.1 Lethal Responses.

The GF and GB vapor-induced lethality for male and female rats are summarized in Tables 2a, 2b, 3a and 3b. The lethality fractions for exposed rats are reported for a given agent vapor concentration and exposure duration. Tables 4 and 5 summarize the fraction of exposed male and female rats in which tremors, convulsions and salivation were recorded. The exposure conditions used in the present study were selected to optimize estimates of the LC_{50} for each duration of exposure.

The results of probit analyses for each sex and duration of exposure are found in the appendix with estimates of LC_{16}, LC_{50}, and LC_{84} provided for each analysis. Male and female 24-hr and 14-day LCt_{50} values with corresponding 95% fiducial limits and slopes are summarized in Tables 6 and 7 respectively.

3.2 Pupil Diameter.

Mean pupil diameters and the Ct ranges for surviving male and female rats having a complete set of six pupil measurements (pre-exposure, 30-60 min post, 1-day post, 2-day post, 7-day post, and 14-day-post) were calculated and are shown in Figure 4. The number (N) of surviving rats was different among the several exposure times. Miosis was observed in both sexes at 1-hr post exposure for all three exposure durations, but this reversed and progressed to mydriasis at 2-day post exposure. Normal (pre-exposure) pupil size was observed at the 14-day post exposure time. An analysis of variance was performed to test whether pupil diameter changed significantly at each successive observation time (Table 8). Except for the pre-exposure and 14-day comparison, the average pupil diameter at each observation time differed from the average pupil size at every other observation time, regardless of exposure duration (by the Tukey multiple comparison test at the .05 level). These data are summarized in Table 9 and plotted in Figure 5. Trends in male and female pupil diameter were similar to patterns observed in rats exposed to GB.[2-3]

4. DISCUSSION

4.1 Literature Overview of GF Inhalation Exposures.

Estimates of GF acute inhalation toxicity have been reported using exposure times not exceeding 10 min.[10-13] The present study extends the scope of exposure conditions by examining exposure times ranging from 10 to 240 min to determine if LCt_{50} changes over time. Thus, it was possible to develop a model for predicting probability of lethality at a given

combination of exposure concentration and time. In addition, a variety of generation and chemical analysis methods were used in previous studies of GF vapor toxicity.[10-13] However, they were limited to the best technology available at the time. The present study is distinguished by utilizing "state-of-the-art" methods that enabled reliable vapor generation and analytical verification of the concentration of a less volatile nerve agent, such as GF, in a dynamic airflow inhalation exposure chamber.

Table 10 summarizes the findings of previous GF vapor toxicity studies including LCt_{50} values, animal species tested and the potency ratio for GF:GB.[10-13] Three out of the four studies establish GF vapor as being more potent than GB vapor for short exposure times, with only Cresthull (1957) reporting GF as being less potent than GB. Similar to the current study, some of the investigators[12-13] also calculated a GB LCt_{50} within the same study while others[10-11] based GF to GB potency comparisons on historical data.

4.2 Formulating an Empirical Lethality Probability Model for the Rat.

The results of multifactor probit analyses for vapor-induced lethality in which the significance of sex, concentration, and agent was tested are shown in Appendix B.

Using binary logistic regression with a normit link function, a full quadratic model (crossed with sex) based on the GF data was initially used to develop the model. The backwards elimination procedure reduced the 12 possible terms to six significant terms ($p<0.05$). For the probability of lethality, let Y = normit (where normit = probit –5). Note that the center of the data is approximately at $C = 8$ mg/m^3 and $t = 50$ min. Logarithms are base 10.

24-hr data (Equation 1)

$$Y = 1.1802 - 0.9115\ Sex + 19.337\ Log\ (C/8) + 15.621\ Log\ (t/50) - 2.9868\ [Log\ (t/50)]^2 - 1.1221\ Sex\ Log\ (C/8)$$

For males (Sex = 1), this reduces to:

$$Y = 0.2687 + 18.2149\ Log\ (C/8) + 15.621\ Log\ (t/50) - 2.9868\ [Log\ (t/50)]^2$$

For females (Sex = –1), this reduces to:

$$Y = 2.0917 + 20.4591\ Log\ (C/8) + 15.621\ Log\ (t/50) - 2.9868\ [Log\ (t/50)]^2$$

14-day data (Equation 2)

$$Y = 1.1587 - 1.0387\ Sex + 19.054\ Log\ (C/8) + 15.474\ Log\ (t/50) + 4.259\ [Log\ (C/8)]^2 - 5.643\ [Log\ (t/50)]^2 - 1.4387\ Sex\ Log\ (C/8)$$

For males (Sex = 1), this reduces to:

$$Y = 0.1200 + 17.6153\ Log\ (C/8) + 15.474\ Log\ (t/50) + 4.259\ [Log\ (C/8)]^2 - 5.643\ [Log\ (t/50)]^2$$

For females (Sex = -1), this reduces to:

$$Y = 2.1974 + 20.4927 \text{ Log } (C/8) + 15.474 \text{ Log } (t/50) + 4.259 [\text{Log } C/8)]^2 - 5.643 [\text{Log } (t/50)]^2$$

4.3 LCt_{50} Curves from Empirical Lethality Probability Model.

Predicted male and female LCt_{50} relationships from Eqns. [1] and [2] are shown in Figures 6 and 7. By observation, linear relationships between Log (LCt_{50}) and Log (t) that would be predicted by other toxicology models, such as Haber's Law or Toxic Load, are not seen. The squares and diamonds on the graph represent the male and female LCt_{50} values, respectively, as determined from individual probit analyses, with the actual values listed in Tables 6 and 7 (along with the corresponding probit slopes). Vertical lines in Figures 6 and 7 represent the 95% fiducial limits[16] for the individual LCt_{50} values.

4.4 Formulating a Lethal Probability Model for Operational Applications (Toxic Load).

For operational purposes (casualty estimation in transport and dispersion models, toxicity data in handbooks, etc.), a simple model is needed (i.e., a first-order model). The empirical model (a higher order fit obtained via a multifactor probit analysis) is too complex for many operational scenarios. A toxic load expression (a first-order model) would be easier to code and implement in operational models than the use of the empirical model. Comparisons of empirical model predictions to predictions obtained via the toxic load expression have been made previously.[2-3] The toxic load model states that $C^n t = k$ or $Y = b_0 + b_1 \text{ Log}(C) + b_2 \text{ Log}(t)$, where the toxic load exponent is the ratio b_2/b_1.

As estimated from the 24-hr GF lethality data, the toxic load exponent (n)= 1.24 and the toxic load models are:

$$L(C^{1.24} t)_{50} = 722 \quad \text{(male rats)}$$
$$L(C^{1.24} t)_{50} = 556 \quad \text{(female rats)}$$

When the probit slope for concentration is allowed to depend on gender, the toxic load exponent (n) becomes 1.17 for males and 1.29 for females.

$$L(C^{1.17} t)_{50} = 630 \quad \text{(male rats)}$$
$$L(C^{1.29} t)_{50} = 621 \quad \text{(female rats)}$$

Extrapolation of the toxic load model beyond 240 min or < 10 min will cause underestimation of the LC_{50}'s and hence overestimation of toxicity. Figures 8 and 9 depict these models.

4.5 Male vs. Female Sensitivity to GF Vapor-Induced Lethality.

Female rats were more sensitive to the lethal effects of GF vapor than males in the present study. A review of the clinical sign data suggests that clinical signs of toxicity appeared earliest in females, and progressed to more severe levels earlier than in male rats. This

observation is consistent with that of others regarding male vs. female differences in sensitivity to CWAs.[17-18,2-3] In particular, Callaway and Blackburn (1954) reported that female rats were nearly twice as sensitive to the lethal effects of GF vapor than males. The reasons for these sex differences are not known but may involve differences in availability or activity of blood cholinesterase levels or absorbed dose (internal dose) of GF vapor between male and female rats. Blood cholinesterase activity and GF regeneration data from this study will be discussed in another report.[19]

4.6 Pupil Response to GF Vapor Exposure.

Since GF vapor concentrations used in this study were selected for estimating the LC_{50}, it was obvious that maximal miosis would be observed for all exposed rats during the first 24 hr following exposure. The consistent reversal of miosis to mydriasis is usually not a common response, but is seen regularly in exposures to organophosphate agents.[2-3] Because the study was designed for lethality, it is difficult to interpret the dose-response relationship for mydriasis. It is therefore unclear whether maximum mydriasis was observed and therefore cannot be determined how it depends on exposure conditions. Possible mechanisms describing organophosphate induced changes in pupil diameter have been discussed by Bito, Hyslop and Hyndman (1967).[20]

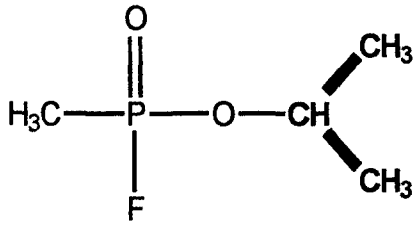
4.7 Potency Ratio.

Relative potencies for GB vs. GF are shown in Tables 11a and 11b. When combining data from GB and GF exposures, the probit analysis routine uses the same slope for both agents.

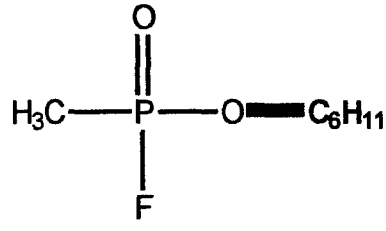
For male and female rats, GB is more toxic than GF at 10 min. At 60 min, GB is less toxic than GF in male rats and equally potent in female rats. At 240 min, GB is less toxic than GF for male and female rats. Females have lower LCt_{50} values than males for both GF and GB at the exposure durations studied, and the LCt_{50} values at 240 min are the highest, regardless of agent or gender.

5. CONCLUSIONS

This study utilized "state-of-the-art" methods that enabled reliable vapor generation and analytical verification of the concentrations for a less volatile nerve agent, such as GF, in a dynamic airflow inhalation exposure chamber. Estimates of LCt_{50} for GF vapor were not constant over times ranging from 10 to 240 min of exposure. Thus, the empirical relationship between exposure concentration, time and probability of lethality in the rat could not adequately be described using Haber's rule. Although curvature in the plot of LCt_{50} vs exposure time was statistically significant, an approximation of that empirical relationship using a toxic load model could be used for operational applications. The relative potency between GF and GB were found to be dependent on exposure duration. Potential applications of these findings include improvements to hazard prediction modeling, setting of CWA detector limits and decontamination standards.



GB (Sarin)
Mol. Wt.: 140.1 g mol-1



GF
Mol. Wt.: 180.2 g mol-1

Figure 1. Structures of GB and GF.

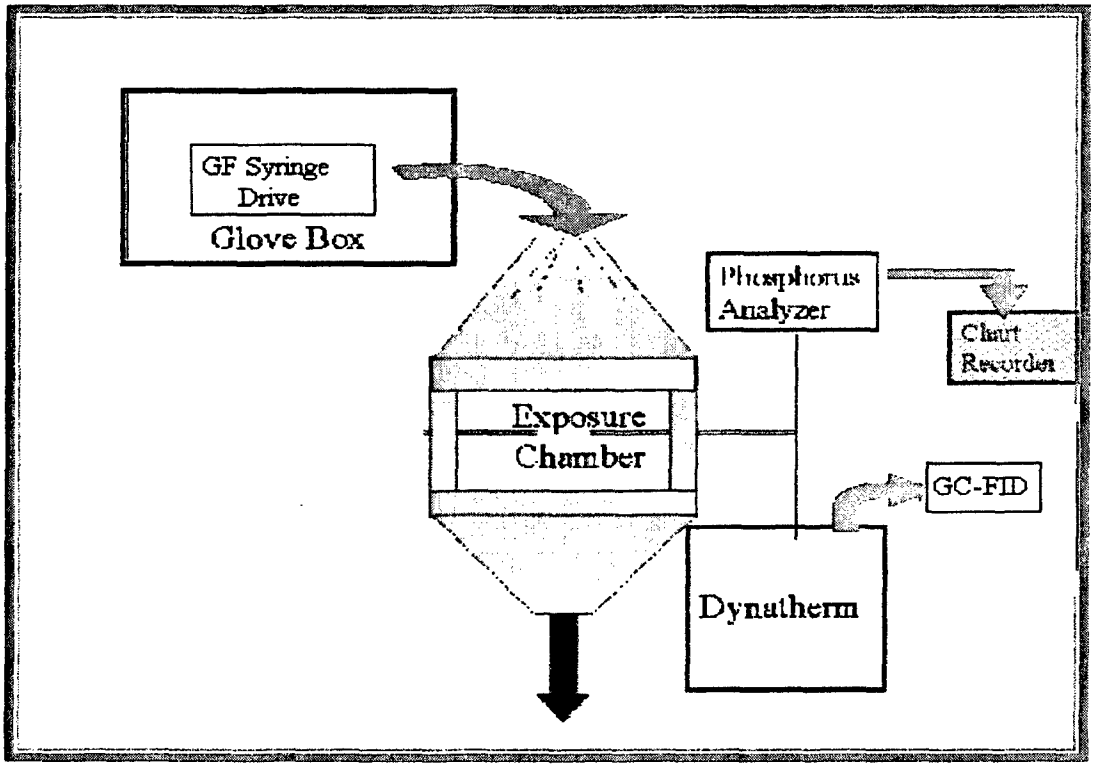


Figure 2. Schematic of Inhalation Exposure Chamber and Vapor Generation System.

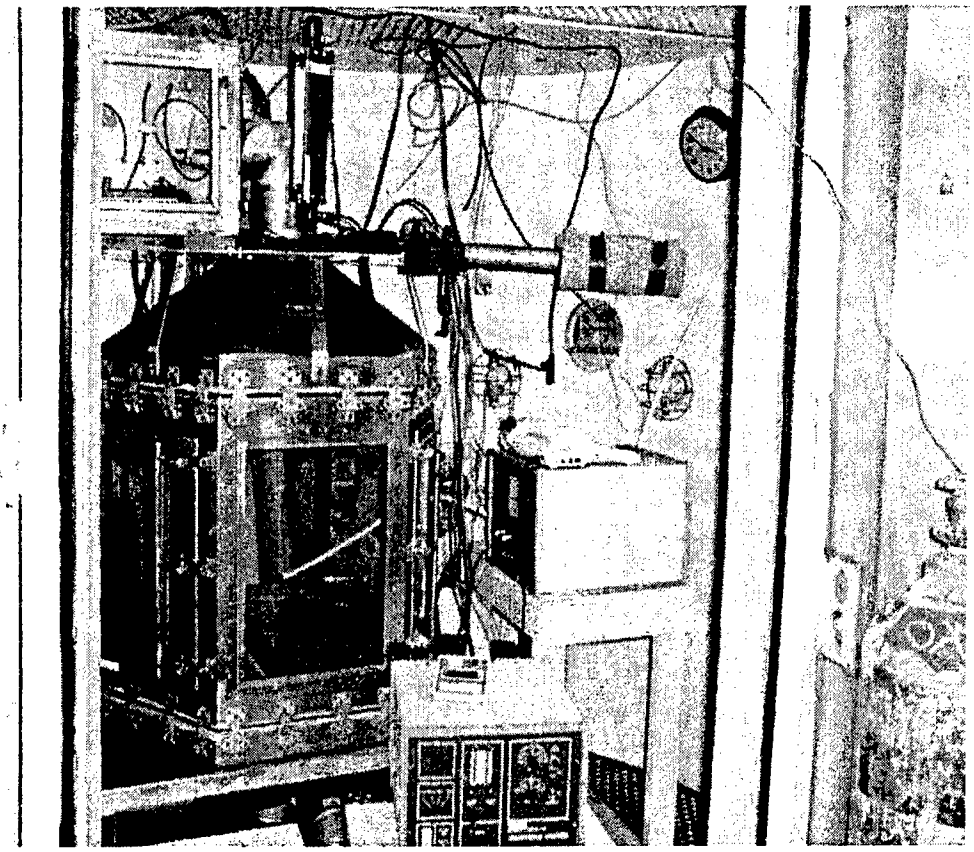


Figure 3. Experimental Exposure Chamber System.

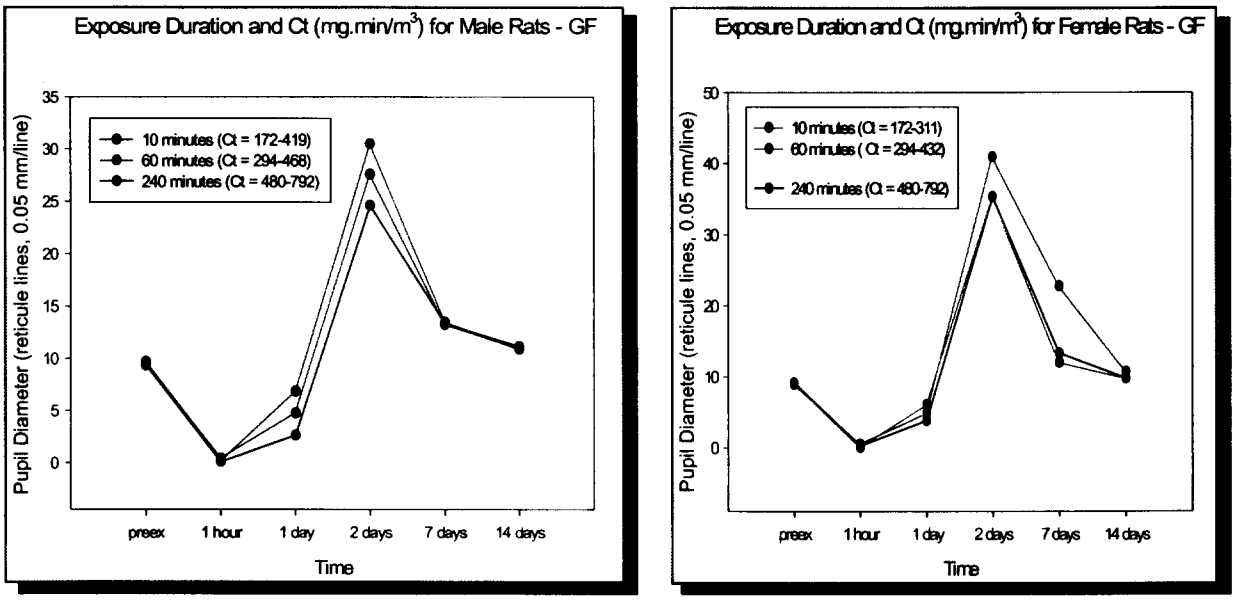


Figure 4. Effects of GF Vapor Exposure on Pupil Diameter.

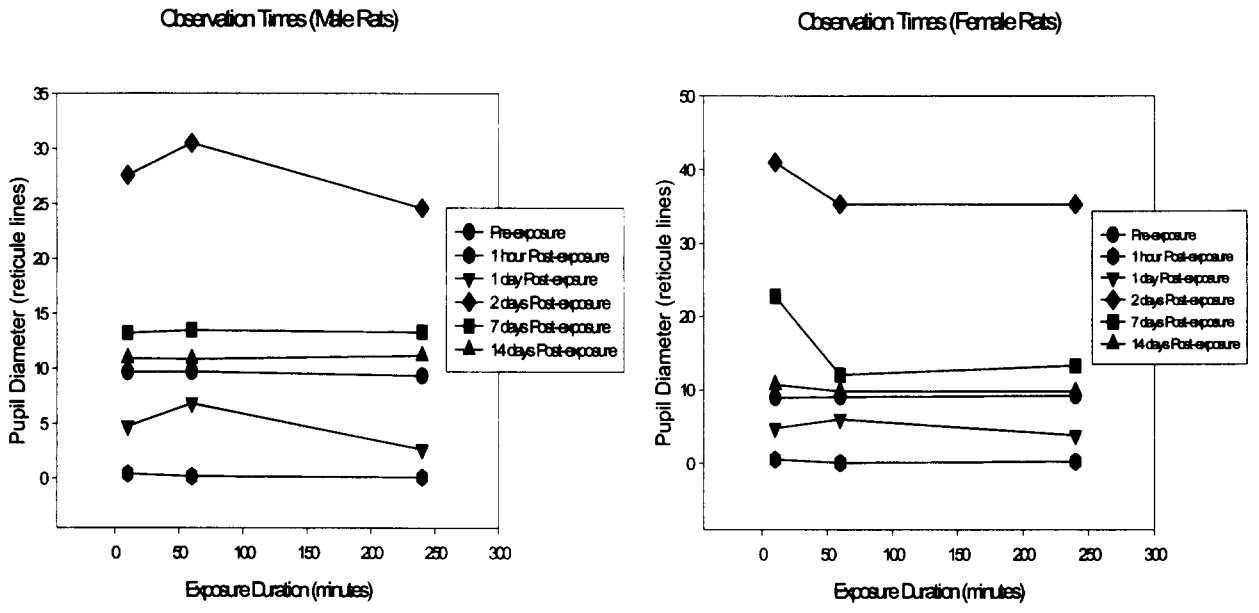


Figure 5. Pupil Diameter vs. GF Vapor Exposure Duration.

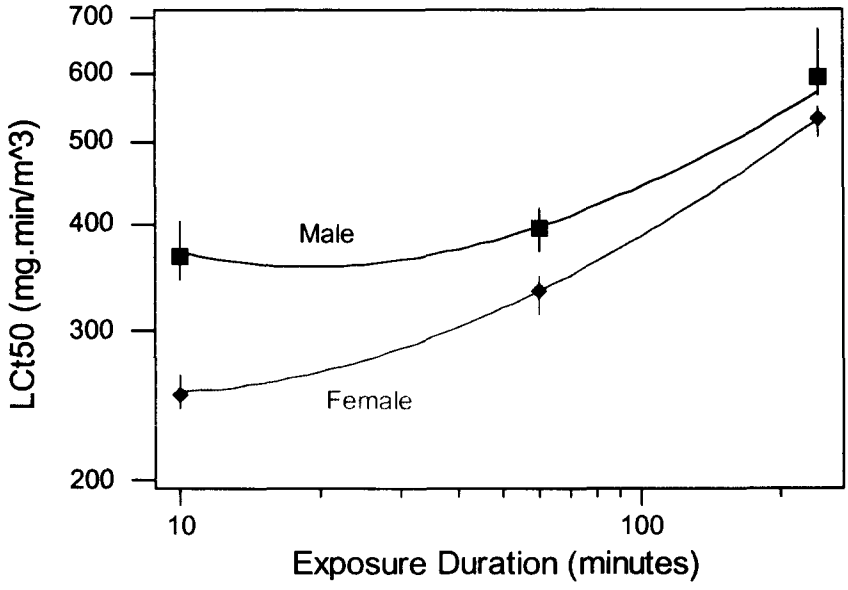


Figure 6. Lethality Within 24-hr From GF Vapor (Vertical Bars Are 95% Fiducial Limits).

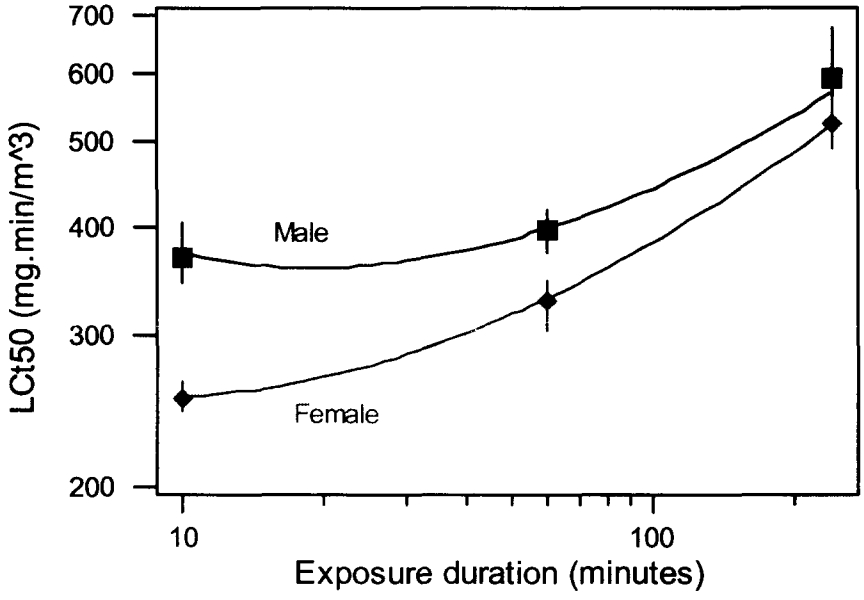


Figure 7. Lethality Within 14 days From GF Vapor (Vertical Bars Are 95% Fiducial Limits).

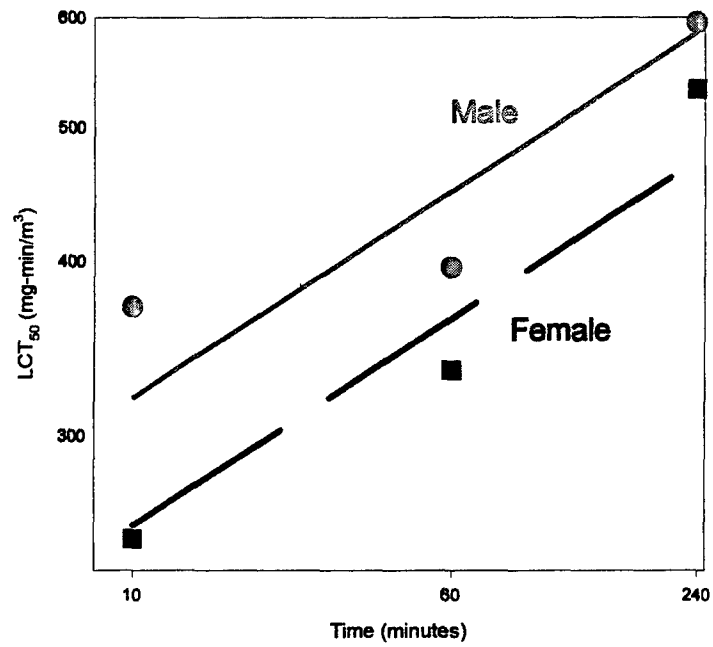


Figure 8. LCt_{50} vs. GF Vapor Exposure Duration for Male and Female Rats 24-hr Post-Exposure – same toxic load exponent (n)

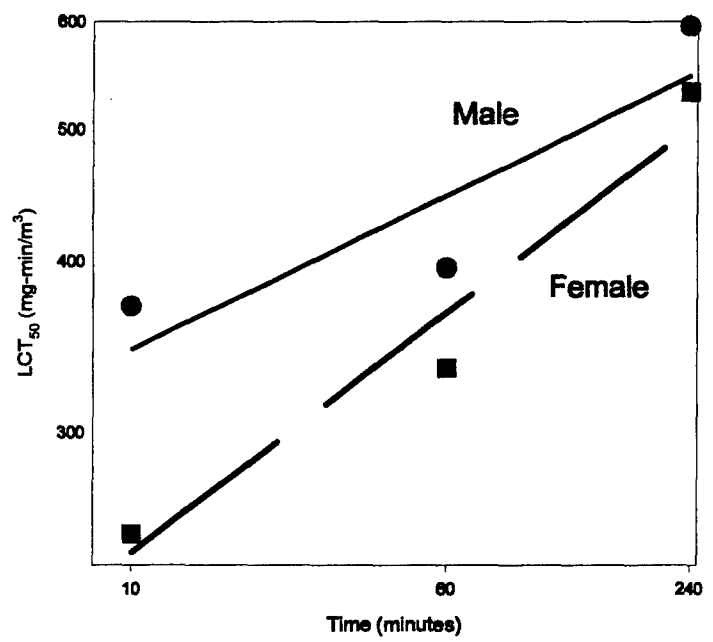


Figure 9. LCt_{50} vs. GF Vapor Exposure Duration for Male and Female Rats 24-hr Post-Exposure – different toxic load exponent (n)

Table 1. Agent Vapor Pressure Comparisons.

Chemical Warfare Agent (CWA)	Vapor Pressure (mm Hg @20C)	Vapor Pressure comparison to GB
GB	2.1	1.0
GF	0.044	0.021
HD	0.072	0.034
VX	0.0007	0.00034

Table 2a. Summary of GF Vapor-Induced Lethality in Male Rats.

Exposure Duration (min)	GF vapor concentration (mg/m^3)	Lethal Fraction of Exposed (24 hr)	(14 days)	Exposure Date
10	17.2	0/10	0/10	4/26/01
	21.5	0/10	0/10	5/9/01
	31.1	1/10	1/10	6/19/01
	34.4	2/10	2/10	7/9/01
	41.9	9/10	9/10	7/26/01
60	4.9	0/10	0/10	4/23/01
	5.7	1/10	1/10	5/3/01
	6.4	4/10	4/10	7/12/01
	7.2	7/10	7/10	6/11/01
	7.8	10/10	10/10	7/31/01
240	2.0	3/10	4/10	5/2/01
	2.0	0/10	0/10	7/10/01
	2.2	2/10	2/10	7/30/01
	2.5	6/10	6/10	6/20/01
	3.3	9/10	9/10	4/25/01

Table 2b. Summary of GB Vapor-Induced Lethality in Male Rats.

Exposure Duration (min)	GB vapor concentration (mg/m^3)	Lethal Fraction of Exposed (24 hr)	(14 days)	Exposure Date
10	22.7	0/10	0/10	7/16/01
	26.7	1/10	2/10	11/14/01
	28.7	4/10	4/10	7/26/01
	32.8	5/10	5/10	10/15/01
	35.9	8/10	10/10	11/05/01
60	6.6	0/5	0/5	4/30/01
	7.0	4/10	4/10	6/18/01
	7.5	4/5	4/5	5/7/01
240	4.3	0/10	0/10	11/13/01
	5.6	7/10	8/10	2/19/02

Table 3a. Summary of GF Vapor-Induced Lethality in Female Rats.

Exposure Duration (min)	GF vapor concentration (mg/m^3)	Lethal Fraction of Exposed (24 hr)	(14 days)	Exposure Date
10	17.2	0/10	0/10	4/26/01
	21.5	0/10	0/10	5/9/01
	23.3	0/10	0/10	7/26/01
	23.9	5/10	5/10	10/1/01
	25.2	6/10	6/10	10/1/01
	26.9	6/10	6/10	7/9/01
	31.1	10/10	10/10	6/19/01
60	4.9	2/10	3/10	4/23/01
	5.7	2/10	2/10	5/3/01
	5.9	9/10	9/10	7/31/01
	6.4	10/10	10/10	7/12/01
	7.2	10/10	10/10	6/11/01
240	2.0	1/10	1/10	5/2/01
	2.0	1/10	3/10	7/10/01
	2.2	7/10	7/10	7/30/01
	2.5	8/10	8/10	6/20/01
	3.3	10/10	10/10	4/25/01

Table 3b. Summary of GB Vapor-Induced Lethality in Female Rats.

Exposure Duration (min)	GB vapor concentration (mg/m^3)	Lethal Fraction of Exposed (24 hr)	(14 days)	Exposure Date
10	18.0	0/10	0/10	7/16/01
	21.6	1/10	1/10	7/26/01
	22.7	2/10	2/10	12/10/01
	23.8	7/10	8/10	11/20/01
	24.8	7/10	7/10	10/31/01
	26.6	10/10	10/10	10/24/01
60	5.6	1/5	1/5	5/7/01
	6.1	6/10	7/10	6/18/01
	6.6	5/5	5/5	4/30/01
240	3.5	5/10	5/10	11/15/01

Table 4. Summary of GF Vapor-Induced Sub-Lethal Effects in Male Rats.

Exposure Duration (min)	GF vapor Conc. (mg/m^3)	Tremors (# / total)	Convulsions (# / total)	Salivation (# / total)	Exposure Date
10	17.2	9/10	0/10	0/10	4/26/01
	21.5	10/10	0/10	1/10	5/9/01
	31.1	10/10	9/10	8/10	6/19/01
	34.4	9/10	5/10	6/10	7/9/01
	41.9	10/10	10/10	10/10	7/26/01
60	4.9	10/10	0/10	2/10	4/23/01
	5.7	10/10	2/10	7/10	5/3/01
	6.4	10/10	9/10	8/10	7/12/01
	7.2	10/10	8/10	3/10	6/11/01
	7.8	10/10	10/10	10/10	7/31/01
240	2.0	10/10	5/10	6/10	5/2/01
	2.0	10/10	6/10	5/10	7/10/01
	2.2	10/10	10/10	10/10	7/30/01
	2.5	10/10	9/10	9/10	6/20/01
	3.3	10/10	10/10	3/10	4/25/01

Table 5. Summary of GF Vapor-Induced Sub-Lethal Effects in Female Rats.

Exposure Duration (min)	GF vapor Conc. (mg/m^3)	Tremors (# / total)	Convulsions (# / total)	Salivation (# / total)	Exposure Date
10	17.2	9/10	1/10	4/10	4/26/01
	21.5	10/10	3/10	5/10	5/9/01
	23.3	10/10	0/10	0/10	7/26/01
	23.9	10/10	7/10	6/10	10/1/01
	25.2	10/10	8/10	7/10	10/1/01
	26.9	10/10	9/10	7/10	7/9/01
	31.1	10/10	10/10	10/10	6/19/01
60	4.9	10/10	3/10	8/10	4/23/01
	5.7	10/10	6/10	5/10	5/3/01
	5.9	10/10	10/10	10/10	7/31/01
	6.4	10/10	10/10	7/10	7/12/01
	7.2	10/10	10/10	7/10	6/11/01
240	2.0	10/10	3/10	2/10	5/2/01
	2.0	10/10	9/10	9/10	7/10/01
	2.2	10/10	10/10	10/10	7/30/01
	2.5	10/10	9/10	7/10	6/20/01
	3.3	10/10	10/10	5/10	4/25/01

Table 6. LC_{50}, LCt_{50}, Slopes and Fiducial Limits for GF and GB Vapor-Induced Lethality (24-hr post exposure) at 10, 60, and 240 min.

Exp.Dur. (min)	Females						Males				
	Agent	LC_{50} (mg/m^3)	LC_{50} 95 %FI (mg/m^3)	LCt_{50} (mg. min/m^3)	LCt_{50} 95 %F.I (mg/m^3)	Slope	LC_{50} (mg/m^3)	LC_{50} 95 %F.I (mg/m^3)	LCt_{50} (mg. min/m^3)	LCt_{50} 95 %F.I (mg/m^3)	Slope
10	GF	25.3	24.5-26.2	253	245-262	31.2	37.1	34.4-40.5	371	344-405	16.9
	GB	23.5	22.8-24.3	235	228-243		31.6	29.7-33.8	316	297-348	
60	GF	5.57	5.29-5.81	334	317-349	25.8	6.60	6.26-6.94	396	376-416	24.4
	GB	5.92	5.54-6.27	355	332-376		7.21	6.81-7.73	433	409-464	
240	GF	2.22	2.11-2.36	533	506-566	22.6	2.48	2.29-2.82	595	550-677	13.3
	GB	3.50	3.19-3.84	840	766-922		5.40	4.80-6.19	1296	1152-1486	

Table 7. LC_{50}, LCt_{50}, Slopes and Fiducial Limits for GF and GB Vapor-Induced Lethality (14-day post exposure) at 10, 60, and 240 min.

Exp.Dur. (min)	Females						Males				
	Agent	LC_{50} (mg/m^3)	LC_{50} 95 %F.I (mg/m^3)	LCt_{50} (mg. min/m^3)	LCt_{50} 95 %F.I (mg/m^3)	Slope	LC_{50} (mg/m^3)	LC_{50} 95 %F.I (mg/m^3)	LCt_{50} (mg. min/m^3)	LCt_{50} 95 %F.I (mg/m^3)	Slope
10	GF	25.2	24.5-26.2	252	245-262	31.4	36.9	34.5-40.0	369	345-400	
	GB	23.4	22.7-24.2	234	227-242		30.4	28.7-32.3	304	287-323	18.8
60	GF	5.49	5.17-5.76	329	310-346	22.4	6.60	6.26-6.94	396	376-416	
	GB	5.81	5.34-6.19	349	320-371		7.21	6.81-7.73	433	409-464	24.4
240	GF	2.18	2.05-2.34	523	492-562	18.5	2.48	2.29-2.82	595	550-677	
	GB	3.50	3.10-3.95	840	744-948		5.24	4.64-6.00	1258	1114-1440	12.90

Table 8. Analysis of Variance of Rat Pupil Diameters for Rats with a Complete Set of Six Pupil Measurements Model: Pupil Diameter versus Observation Time (OT) and Rat.

Factor	Type	Levels
OT	fixed	6
Rat	random	172

Analysis of Variance for Pupil Diameter, using Adjusted SS for Tests

Source	DF	Seq SS	Adj SS	Adj MS	F	P
OT	5	108545.2	108545.2	21709.0	463.02	0.000
Rat	171	12889.1	12889.1	75.4	1.61	0.000
OT*Rat	855	40087.7	40087.7	46.9		
Total	1031	161521.9				

Bonferroni Simultaneous Tests
Response Variable Pupil Diameter
All Pairwise Comparisons among Levels of OT

OT = 14day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
1day	-5.90	0.7384	-7.98	0.0000
2day	21.84	0.7384	29.58	0.0000
7day	4.90	0.7384	6.64	0.0000
post	-10.37	0.7384	-14.05	0.0000
pre	-1.29	0.7384	-1.75	1.0000

OT = 1day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
2day	27.738	0.7384	37.567	0.0000
7day	10.797	0.7384	14.622	0.0000
post	-4.477	0.7384	-6.063	0.0000
pre	4.605	0.7384	6.236	0.0000

OT = 2day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
7day	-16.94	0.7384	-22.94	0.0000
post	-32.22	0.7384	-43.63	0.0000
pre	-23.13	0.7384	-31.33	0.0000

OT = 7day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
post	-15.27	0.7384	-20.69	0.0000
pre	-6.19	0.7384	-8.39	0.0000

OT = post subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
pre	9.081	0.7384	12.30	0.0000

Sidak Simultaneous Tests
Response Variable Pupil Diameter
All Pairwise Comparisons among Levels of OT

Table 8. Analysis of Variance of Rat Pupil Diameters for Rats with a Complete Set of Six Pupil Measurements Model: Pupil Diameter versus Observation Time (OT) and Rat (Continued).

OT = 14day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
1day	-5.90	0.7384	-7.98	0.0000
2day	21.84	0.7384	29.58	0.0000
7day	4.90	0.7384	6.64	0.0000
post	-10.37	0.7384	-14.05	0.0000
pre	-1.29	0.7384	-1.75	0.7175

OT = 1day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
2day	27.738	0.7384	37.567	0.0000
7day	10.797	0.7384	14.622	0.0000
post	-4.477	0.7384	-6.063	0.0000
pre	4.605	0.7384	6.236	0.0000

OT = 2day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
7day	-16.94	0.7384	-22.94	0.0000
post	-32.22	0.7384	-43.63	0.0000
pre	-23.13	0.7384	-31.33	0.0000

OT = 7day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
post	-15.27	0.7384	-20.69	0.0000
pre	-6.19	0.7384	-8.39	0.0000

OT = post subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
pre	9.081	0.7384	12.30	0.0000

Tukey Simultaneous Tests
Response Variable Pupil Diameter
All Pairwise Comparisons among Levels of OT

OT = 14day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
1day	-5.90	0.7384	-7.98	0.0000
2day	21.84	0.7384	29.58	0.0000
7day	4.90	0.7384	6.64	0.0000
post	-10.37	0.7384	-14.05	0.0000
pre	-1.29	0.7384	-1.75	0.4998

Table 8. Analysis of Variance of Rat Pupil Diameters for Rats with a Complete Set of Six Pupil Measurements Model: Pupil Diameter versus Observation Time (OT) and Rat (Continued).

OT = 1day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
2day	27.738	0.7384	37.567	0.0000
7day	10.797	0.7384	14.622	0.0000
post	-4.477	0.7384	-6.063	0.0000
pre	4.605	0.7384	6.236	0.0000

OT = 2day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
7day	-16.94	0.7384	-22.94	0.0000
post	-32.22	0.7384	-43.63	0.0000
pre	-23.13	0.7384	-31.33	0.0000

OT = 7day subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
post	-15.27	0.7384	-20.69	0.0000
pre	-6.19	0.7384	-8.39	0.0000

OT = post subtracted from:

Level OT	Difference of Means	SE of Difference	T-Value	Adjusted P-Value
pre	9.081	0.7384	12.30	0.0000

Table 9. Mean Pupil Diameters (in Reticule Lines, 1 line = 0.05mm) and Standard Errors for Surviving Rats Having a Complete Set of Six Pupil Measurements.

Exposure Time (min)	Observation Time	Female			Male		
		Rats	Mean PD	Stnd Err	Rats	Mean PD	Stnd Err
10	pre-exp	43	9.02	0.34	36	9.67	0.23
10	30-60 min		0.53	0.07		0.42	0.08
10	1 day		4.83	0.49		4.76	0.53
10	2 days		40.98	1.68		27.58	1.52
10	7 days		22.74	3.20		13.22	0.65
10	14 days		10.74	0.49		10.92	0.40
60	pre-exp	15	9.07	0.48	28	9.70	0.36
60	30-60 min		0.07	0.05		0.18	0.05
60	1 day		6.07	0.83		6.84	1.05
60	2 days		35.33	2.59		30.50	1.86
60	7 days		12.07	0.91		13.50	0.74
60	14 days		9.80	0.79		10.86	0.50
240	pre-exp	21	9.19	0.35	29	9.34	0.31
240	30-60 min		0.26	0.08		0.10	0.04
240	1 day		3.86	0.76		2.65	0.51
240	2 days		35.29	2.91		24.60	1.92
240	7 days		13.33	1.02		13.31	0.84
240	14 days		9.81	0.53		11.17	0.45

Table 10. Historical Overview of GF Inhalation Exposures.

Investigator	Species	Exp. Dur (min)	GF LCt_{50}	Conf. limits	Potency ratio GF/GB
Muir	Rat	10	249	181-349	0.8
McGrath	Guinea Pig	10	165	147-179	0.8
	Mice	10	280	200-300	0.74
Cresthull	Monkey	10	130	112-151	1.79
		2	75	63-87	1.76
Calloway	Rat (male)	1	181	169-192	0.92
	Rat (female)	1	110	93-130	0.81

Table 11a. Relative Potency for GB vs. GF (whole-body rats) – 24-hr data.

Exposure Duration (min)	Gender	Relative Potency GF/GB	95% F.I
10	Male	1.17	1.06-1.30
	Female	1.07	1.03-1.13
60	Male	0.92	0.84-0.99
	Female	0.94	0.87-1.02
240	Male	0.46	0.39-0.53
	Female	0.63	0.57-0.71

Table 11b. Relative Potency for GB vs. GF (whole-body rats) – 14-day data.

Exposure Duration (min)	Gender	Relative Potency GF/GB	95% F.I
10	Male	1.21	1.11-1.34
	Female	1.08	1.03-1.13
60	Male	0.92	0.84-0.99
	Female	0.95	0.87-1.04
240	Male	0.46	0.40-0.54
	Female	0.62	0.55-0.72

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APPENDIX A

PROBIT ANALYSES

Female Rats, 10 min GF and GB Exposures, 24-hr Deaths A-2

Female Rats, 10 min GF and GB Exposures, 14-Day Deaths A-4

Female Rats, 60 min GF and GB Exposures, 24-hr Deaths A-6

Female Rats, 60 min GF and GB Exposures, 14-Day Deaths A-8

Female Rats, 240 min GF and GB Exposures, 24-hr Deaths A-10

Female Rats, 240 min GF and GB Exposures, 14-Day Deaths A-12

Male Rats, 10 min GF and GB Exposures, 24-hr Deaths A-14

Male Rats, 10 min GF and GB Exposures, 14-Day Deaths A-16

Male Rats, 60 min GF and GB Exposures, 24-hr and 14-Day Deaths A-18

Male Rats, 240 min GF and GB Exposures, 24-hr Deaths A-20

Male Rats, 240 min GF and GB Exposures, 14-Day Deaths A-22

Female Rats, 10 min GF and GB Exposures, 24-hr Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 1d	Success	54
	Failure	76
Exposed	Total	130

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-42.789	7.717	-5.54	0.000
Conc	31.193	5.619	5.55	0.000
Agent				
GF	-0.9528	0.3226	-2.95	0.003
Natural Response	0.000			

Test for equal slopes: Chi-Square = 1.0068, DF = 1, P-Value = 0.316
Log-Likelihood = -46.973

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	11.257	10	0.338
Deviance	12.218	10	0.271
Hosmer-Lemeshow	2.000	5	0.849

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group							
Value	1	2	3	4	5	6	7	Total
Success								
Obs	0	1	5	8	14	16	10	54
Exp	0.0	1.4	3.7	8.0	13.2	17.6	10.0	
Failure								
Obs	20	19	15	12	6	4	0	76
Exp	20.0	18.6	16.3	12.0	6.8	2.4	0.0	
Total	20	20	20	20	20	20	10	130

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.37175	0.00670	1.35861	1.38488
Scale	0.032058	0.005775	0.022522	0.045633

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	23.6010	0.3642	22.8978	24.3258
Standard Deviation	1.7445	0.3172	1.2216	2.4914
Interquartile Range(IQR)	2.3447	0.4232	1.6461	3.3398

	Estimate	Standard Error	.95.0% Fiducial CI Lower	Upper
Median	23.5368	0.3632	22.7799	24.3014
First Quartile(Q1)	22.3937	0.4048	21.3860	23.1020
Third Quartile(Q3)	24.7384	0.4359	23.9884	25.8576

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	21.8709	0.4509	20.6936	22.6207
50	23.5368	0.3632	22.7799	24.3014
84	25.3296	0.5072	24.5061	26.7147

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.40229	0.00687	1.38883	1.41575
Scale	0.032058	0.005775	0.022522	0.045633

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	25.3207	0.4056	24.5380	26.1282
Standard Deviation	1.8716	0.3465	1.3021	2.6904
Interquartile Range(IQR)	2.5155	0.4624	1.7545	3.6066

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	25.2518	0.3993	24.4827	26.1635
First Quartile(Q1)	24.0253	0.4013	23.0801	24.7693
Third Quartile(Q3)	26.5408	0.5187	25.6886	27.9395

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	23.4645	0.4383	22.3612	24.2225
50	25.2518	0.3993	24.4827	26.1635
84	27.1752	0.6081	26.2181	28.8931

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	1.0729	1.0268	1.1269

Female Rats, 10 min GF and GB Exposures, 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	55
	Failure	75
Exposed	Total	130

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-43.014	7.773	-5.53	0.000
Conc	31.408	5.664	5.55	0.000
Agent				
GF	-1.0280	0.3260	-3.15	0.002
Natural Response	0.000			

Test for equal slopes: Chi-Square = 1.1065, DF = 1, P-Value = 0.293
Log-Likelihood = -46.675

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	12.841	10	0.233
Deviance	13.832	10	0.181
Hosmer-Lemeshow	2.543	5	0.770

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group							
Value	1	2	3	4	5	6	7	Total
Success								
Obs	0	1	5	8	15	16	10	55
Exp	0.0	1.5	3.6	8.3	13.7	17.7	10.0	
Failure								
Obs	20	19	15	12	5	4	0	75
Exp	20.0	18.5	16.4	11.7	6.3	2.3	0.0	
Total	20	20	20	20	20	20	10	130

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.36951	0.00670	1.35639	1.38264
Scale	0.031839	0.005742	0.022359	0.045338

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	23.4791	0.3613	22.7815	24.1980
Standard Deviation	1.7236	0.3128	1.2077	2.4598
Interquartile Range(IQR)	2.3167	0.4174	1.6275	3.2978

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	23.4161	0.3611	22.6538	24.1663
First Quartile(Q1)	22.2863	0.4078	21.2637	22.9948
Third Quartile(Q3)	24.6030	0.4260	23.8632	25.6865

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	21.7696	0.4548	20.5765	22.5224
50	23.4161	0.3611	22.6538	24.1663
84	25.1870	0.4941	24.3796	26.5272

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.40224	0.00683	1.38886	1.41563
Scale	0.031839	0.005742	0.022359	0.045338

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	25.3170	0.4032	24.5389	26.1197
Standard Deviation	1.8585	0.3444	1.2926	2.6723
Interquartile Range(IQR)	2.4980	0.4596	1.7418	3.5827

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	25.2490	0.3970	24.4840	26.1555
First Quartile(Q1)	24.0309	0.3992	23.0899	24.7709
Third Quartile(Q3)	26.5289	0.5154	25.6819	27.9190

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	23.4737	0.4361	22.3752	24.2278
50	25.2490	0.3970	24.4840	26.1555
84	27.1586	0.6042	26.2077	28.8658

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	1.0783	1.0324	1.1330

Female Rats, 60 min GF and GB Exposures, 24-hr Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 1d	Success	45
	Failure	25
Exposed	Total	70

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-19.959	4.578	-4.36	0.000
Conc	25.843	5.849	4.42	0.000
Agent				
GF	0.6887	0.4228	1.63	0.103
Natural Response	0.000			

Test for equal slopes: Chi-Square = 0.7578, DF = 1, P-Value = 0.384
Log-Likelihood = -28.775

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	11.748	5	0.038
Deviance	12.568	5	0.028
Hosmer-Lemeshow	9.900	4	0.042

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	2	3	6	9	15	10	45
Exp	0.8	7.4	6.3	7.4	13.9	10.0	
Failure							
Obs	8	12	4	1	0	0	25
Exp	9.2	7.6	3.7	2.6	1.1	0.0	
Total	10	15	10	10	15	10	70

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.77234	0.01218	0.74847	0.79621
Scale	0.038696	0.008758	0.024832	0.060300

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.9438	0.1653	5.6284	6.2768
Standard Deviation	0.5306	0.1201	0.3405	0.8269
Interquartile Range(IQR)	0.7120	0.1594	0.4591	1.1043

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.9202	0.1660	5.5406	6.2658
First Quartile(Q1)	5.5749	0.1842	5.0731	5.8921
Third Quartile(Q3)	6.2869	0.1834	5.9527	6.7734

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	5.4182	0.2002	4.8465	5.7450
50	5.9202	0.1660	5.5406	6.2658
84	6.4688	0.2057	6.1247	7.0674

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.745689	0.009391	0.727283	0.764095
Scale	0.038696	0.008758	0.024832	0.060300

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.5900	0.1194	5.3609	5.8289
Standard Deviation	0.4991	0.1127	0.3205	0.7771
Interquartile Range(IQR)	0.6696	0.1497	0.4321	1.0377

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.5679	0.1204	5.2860	5.8128
First Quartile(Q1)	5.2431	0.1450	4.8274	5.4804
Third Quartile(Q3)	5.9127	0.1375	5.6718	6.2919

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	5.0957	0.1639	4.6053	5.3511
50	5.5679	0.1204	5.2860	5.8128
84	6.0837	0.1615	5.8258	6.5762

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.9405	0.8717	1.0154

Female Rats, 60 min GF and GB Exposures, 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	47
	Failure	23
Exposed	Total	70

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-17.116	4.115	-4.16	0.000
Conc	22.402	5.262	4.26	0.000
Agent				
GF	0.5398	0.4156	1.30	0.194
Natural Response	0.000			

Test for equal slopes: Chi-Square = 1.5194, DF = 1, P-Value = 0.218
Log-Likelihood = -30.291

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	13.898	5	0.016
Deviance	14.635	5	0.012
Hosmer-Lemeshow	12.231	4	0.016

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	3	3	7	9	15	10	47
Exp	1.3	8.2	6.8	7.6	13.8	10.0	
Failure							
Obs	7	12	3	1	0	0	23
Exp	8.7	6.8	3.2	2.4	1.2	0.0	
Total	10	15	10	10	15	10	70

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.76405	0.01443	0.73577	0.79234
Scale	0.04464	0.01049	0.02817	0.07074

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.8391	0.1909	5.4768	6.2254
Standard Deviation	0.6018	0.1398	0.3816	0.9489
Interquartile Range(IQR)	0.8060	0.1846	0.5145	1.2627

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.8084	0.1930	5.3418	6.1941
First Quartile(Q1)	5.4193	0.2199	4.7953	5.7867
Third Quartile(Q3)	6.2253	0.2058	5.8358	6.7605

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	5.2440	0.2397	4.5372	5.6261
50	5.8084	0.1930	5.3418	6.1941
84	6.4335	0.2296	6.0407	7.0997

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.73996	0.01054	0.71930	0.76062
Scale	0.04464	0.01049	0.02817	0.07074

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.5240	0.1313	5.2725	5.7875
Standard Deviation	0.5693	0.1331	0.3600	0.9002
Interquartile Range(IQR)	0.7625	0.1757	0.4854	1.1979

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.4949	0.1334	5.1700	5.7600
First Quartile(Q1)	5.1268	0.1662	4.6318	5.3921
Third Quartile(Q3)	5.8893	0.1511	5.6240	6.3137

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	4.9610	0.1893	4.3764	5.2498
50	5.4949	0.1334	5.1700	5.7600
84	6.0863	0.1801	5.8014	6.6535

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.9460	0.8687	1.0361

Female Rats, 240 min GF and GB Exposures, 24-hr Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 1d	Success	32
	Failure	28
Exposed	Total	60

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-12.298	3.361	-3.66	0.000
Conc	22.605	6.134	3.68	0.000
Agent				
GF	4.488	1.352	3.32	0.001
Natural Response	0.000			

Test for equal slopes: Chi-Square = 1.417461E-22, DF = 1, P-Value = 1.000
Log-Likelihood = -26.161

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	3.225	2	0.199
Deviance	3.230	2	0.199
Hosmer-Lemeshow	3.225	3	0.358

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group					
Value	1	2	3	4	5	Total
Success						
Obs	2	7	5	8	10	32
Exp	3.1	4.7	5.0	8.8	10.0	
Failure						
Obs	18	3	5	2	0	28
Exp	16.9	5.3	5.0	1.2	0.0	
Total	20	10	10	10	10	60

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.54407	0.01753	0.50970	0.57843
Scale	0.04424	0.01201	0.02599	0.07530

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	3.5182	0.1424	3.2499	3.8086
Standard Deviation	0.3593	0.1001	0.2081	0.6202
Interquartile Range(IQR)	0.4813	0.1323	0.2809	0.8248

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	3.5000	0.1413	3.1878	3.8428
First Quartile(Q1)	3.2676	0.1453	2.8591	3.5374
Third Quartile(Q3)	3.7489	0.1667	3.4630	4.2845

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	3.1628	0.1545	2.6956	3.4260
50	3.5000	0.1413	3.1878	3.8428
84	3.8731	0.1892	3.5756	4.5445

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.34551	0.01047	0.32499	0.36603
Scale	0.04424	0.01201	0.02599	0.07530

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	2.2272	0.05547	2.1211	2.3386
Standard Deviation	0.2275	0.06417	0.1309	0.3954
Interquartile Range(IQR)	0.3047	0.08480	0.1766	0.5257

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	2.2157	0.05342	2.1111	2.3631
First Quartile(Q1)	2.0686	0.05562	1.9016	2.1660
Third Quartile(Q3)	2.3733	0.07995	2.2567	2.6776

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	2.0022	0.06436	1.7885	2.1029
50	2.2157	0.05342	2.1111	2.3631
84	2.4519	0.09931	2.3153	2.8581

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.6331	0.5722	0.7117

Female Rats, 240 min GF and GB Exposures, 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	34
	Failure	26
Exposed	Total	60

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-10.048	3.099	-3.24	0.001
Conc	18.468	5.649	3.27	0.001
Agent				
GF	3.799	1.270	2.99	0.003
Natural Response	0.000			

Test for equal slopes: Chi-Square = 5.093617E-22, DF = 1, P-Value = 1.000
Log-Likelihood = -28.932

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	1.741	2	0.419
Deviance	1.759	2	0.415
Hosmer-Lemeshow	1.741	3	0.628

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group					
Value	1	2	3	4	5	Total
Success						
Obs	4	5	7	8	10	34
Exp	4.9	5.0	5.3	8.6	10.0	
Failure						
Obs	16	5	3	2	0	26
Exp	15.1	5.0	4.7	1.4	0.0	
Total	20	10	10	10	10	60

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.54407	0.02146	0.50201	0.58613
Scale	0.05415	0.01656	0.02973	0.09861

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	3.5273	0.1751	3.2003	3.8878
Standard Deviation	0.4415	0.1399	0.2373	0.8216
Interquartile Range(IQR)	0.5893	0.1830	0.3207	1.0832

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	3.5000	0.1729	3.1011	3.9502
First Quartile(Q1)	3.2177	0.1792	2.6569	3.5461
Third Quartile(Q3)	3.8071	0.2121	3.4545	4.6106

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	3.0919	0.1926	2.4390	3.4105
50	3.5000	0.1729	3.1011	3.9502
84	3.9620	0.2468	3.5918	5.0225

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.33837	0.01186	0.31512	0.36162
Scale	0.05415	0.01656	0.02973	0.09861

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	2.1966	0.06208	2.0782	2.3217
Standard Deviation	0.2749	0.08724	0.1476	0.5121
Interquartile Range(IQR)	0.3670	0.1141	0.1995	0.6750

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	2.1796	0.05953	2.0499	2.3445
First Quartile(Q1)	2.0038	0.07070	1.7470	2.1158
Third Quartile(Q3)	2.3708	0.09395	2.2381	2.7919

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	1.9254	0.08490	1.5936	2.0478
50	2.1796	0.05953	2.0499	2.3445
84	2.4673	0.1215	2.3078	3.0668

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.6227	0.5454	0.7193

Male Rats, 10 min GF and GB Exposures, 24-hr Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 1d	Success	30
	Failure	70
Exposed	Total	100

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-25.392	5.005	-5.07	0.000
Conc	16.937	3.357	5.05	0.000
Agent				
GF	-1.1826	0.4120	-2.87	0.004
Natural Response	0.000			

Test for equal slopes: Chi-Square = 0.7477, DF = 1, P-Value = 0.387
Log-Likelihood = -34.879

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	2.894	7	0.895
Deviance	2.915	7	0.893
Hosmer-Lemeshow	2.894	8	0.941

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group										
Value	1	2	3	4	5	6	7	8	9	10	Total
Success											
Obs	0	0	0	1	1	4	2	5	9	8	30
Exp	0.0	0.0	0.1	1.0	1.1	2.4	2.9	6.1	8.2	8.3	
Failure											
Obs	10	10	10	9	9	6	8	5	1	2	70
Exp	10.0	10.0	9.9	9.0	8.9	7.6	7.1	3.9	1.8	1.7	
Total	10	10	10	10	10	10	10	10	10	10	100

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.49919	0.01307	1.47357	1.52481
Scale	0.05904	0.01170	0.04003	0.08707

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	31.8567	0.9830	29.9871	33.8428
Standard Deviation	4.3509	0.9150	2.8811	6.5705
Interquartile Range(IQR)	5.7966	1.1907	3.8754	8.6701

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	31.5636	0.9500	29.7217	33.7902
First Quartile(Q1)	28.7982	0.9435	26.5033	30.5325
Third Quartile(Q3)	34.5947	1.2940	32.5216	38.3261

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	27.5723	1.0257	24.9078	29.3244
50	31.5636	0.9500	29.7217	33.7902
84	36.1327	1.5601	33.7582	40.9058

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.56901	0.01649	1.53668	1.60134
Scale	0.05904	0.01170	0.04003	0.08707

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	37.4130	1.4527	34.6714	40.3713
Standard Deviation	5.1098	1.0937	3.3590	7.7731
Interquartile Range(IQR)	6.8076	1.4240	4.5180	10.2575

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	37.0689	1.4079	34.4002	40.4526
First Quartile(Q1)	33.8210	1.3172	30.8047	36.3990
Third Quartile(Q3)	40.6286	1.8301	37.6617	45.8575

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	32.3814	1.3673	29.0300	34.8627
50	37.0689	1.4079	34.4002	40.4526
84	42.4349	2.1380	39.1321	48.8964

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	1.1744	1.0633	1.3031

Male Rats, 10 min GF and GB Exposures, 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	33
	Failure	67
Exposed	Total	100

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-27.861	5.248	-5.31	0.000
Conc	18.786	3.545	5.30	0.000
Agent				
GF	-1.5866	0.4460	-3.56	0.000
Natural Response	0.000			

Test for equal slopes: Chi-Square = 0.2113, DF = 1, P-Value = 0.646
Log-Likelihood = -32.959

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	4.920	7	0.670
Deviance	5.575	7	0.590
Hosmer-Lemeshow	4.920	8	0.766

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

					Group						
Value	1	2	3	4	5	6	7	8	9	10	Total
Success											
Obs	0	0	0	1	2	2	4	5	9	10	33
Exp	0.0	0.0	0.1	0.8	1.4	2.8	3.2	7.3	8.5	9.1	
Failure											
Obs	10	10	10	9	8	8	6	5	1	0	67
Exp	10.0	10.0	9.9	9.2	8.6	7.2	6.8	2.7	1.5	0.9	
Total	10	10	10	10	10	10	10	10	10	10	100

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.48302	0.01197	1.45957	1.50648
Scale	0.05323	0.01004	0.03677	0.07705

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	30.6398	0.8541	29.0106	32.3605
Standard Deviation	3.7696	0.7411	2.5641	5.5417
Interquartile Range(IQR)	5.0338	0.9706	3.4496	7.3455

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	30.4105	0.8380	28.7342	32.2779
First Quartile(Q1)	27.9976	0.8624	25.9053	29.5619
Third Quartile(Q3)	33.0314	1.0736	31.2467	35.9488

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	26.9209	0.9361	24.5213	28.5179
50	30.4105	0.8380	28.7342	32.2779
84	34.3526	1.2704	32.3531	38.0219

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	1.56748	0.01523	1.53763	1.59732
Scale	0.05323	0.01004	0.03677	0.07705

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	37.2168	1.3276	34.7037	39.9120
Standard Deviation	4.5787	0.9253	3.0813	6.8039
Interquartile Range(IQR)	6.1143	1.2126	4.1452	9.0190

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	36.9383	1.2952	34.4765	39.9879
First Quartile(Q1)	34.0074	1.2169	31.2732	36.3996
Third Quartile(Q3)	40.1218	1.6373	37.4196	44.6208

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	32.6996	1.2557	29.6954	35.0040
50	36.9383	1.2952	34.4765	39.9879
84	41.7265	1.8856	38.7528	47.1839

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	1.2147	1.1102	1.3389

Male Rats, 60 min GF and GB Exposures, 24-hr and 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	30
	Failure	40
Exposed	Total	70

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-20.907	4.661	-4.49	0.000
Conc	24.362	5.482	4.44	0.000
Agent				
GF	0.9388	0.4186	2.24	0.025
Natural Response	0.000			

Test for equal slopes: Chi-Square = 1.6547, DF = 1, P-Value = 0.198
Log-Likelihood = -27.497

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	3.232	5	0.664
Deviance	4.350	5	0.500
Hosmer-Lemeshow	0.920	4	0.922

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	0	1	4	4	11	10	30
Exp	0.0	0.6	4.6	3.8	11.5	9.6	
Failure							
Obs	10	9	11	6	4	0	40
Exp	10.0	9.4	10.4	6.2	3.5	0.4	
Total	10	10	15	10	15	10	70

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.85817	0.01258	0.83351	0.88284
Scale	0.041047	0.009236	0.026409	0.063798

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	7.2462	0.2130	6.8406	7.6759
Standard Deviation	0.6864	0.1612	0.4332	1.0876
Interquartile Range(IQR)	0.9204	0.2136	0.5840	1.4506

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	7.2139	0.2090	6.8069	7.7288
First Quartile(Q1)	6.7684	0.2031	6.2716	7.1605
Third Quartile(Q3)	7.6888	0.2653	7.2603	8.4888

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	6.5668	0.2151	5.9965	6.9472
50	7.2139	0.2090	6.8069	7.7288
84	7.9249	0.3070	7.4557	8.9109

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.81964	0.01035	0.79935	0.83992
Scale	0.041047	0.009236	0.026409	0.063798

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	6.6310	0.1578	6.3287	6.9477
Standard Deviation	0.6281	0.1432	0.4018	0.9819
Interquartile Range(IQR)	0.8422	0.1897	0.5416	1.3097

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	6.6014	0.1573	6.2578	6.9445
First Quartile(Q1)	6.1937	0.1764	5.7107	6.4958
Third Quartile(Q3)	7.0360	0.1909	6.7137	7.5830

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	6.0092	0.1966	5.4402	6.3255
50	6.6014	0.1573	6.2578	6.9445
84	7.2520	0.2247	6.9008	7.9527

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.9151	0.8368	0.9871

Male Rats, 240 min GF and GB Exposures, 24-hr Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 1d	Success	27
	Failure	43
Exposed	Total	70

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-9.735	2.045	-4.76	0.000
Conc	13.295	2.832	4.69	0.000
Agent				
GF	4.541	1.065	4.26	0.000
Natural Response	0.000			

Test for equal slopes: Chi-Square = 2.2632, DF = 1, P-Value = 0.132
Log-Likelihood = -31.376

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	2.877	3	0.411
Deviance	3.657	3	0.301
Hosmer-Lemeshow	2.877	4	0.579

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

			Group				
Value	1	2	3	4	5	6	Total
Success							
Obs	0	3	2	6	7	9	27
Exp	0.9	2.3	2.6	5.4	5.8	9.6	
Failure							
Obs	10	17	8	4	3	1	43
Exp	9.1	17.7	7.4	4.6	4.2	0.4	
Total	10	20	10	10	10	10	70

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.73222	0.02550	0.68224	0.78220
Scale	0.07522	0.01602	0.04954	0.11419

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.4794	0.3293	4.8704	6.1644
Standard Deviation	0.9561	0.2290	0.5980	1.5288
Interquartile Range(IQR)	1.2640	0.2921	0.8036	1.9881

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.3978	0.3169	4.8000	6.1882
First Quartile(Q1)	4.8027	0.2875	4.1543	5.3878
Third Quartile(Q3)	6.0667	0.4092	5.4066	7.2907

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	4.5438	0.2903	3.8446	5.0905
50	5.3978	0.3169	4.8000	6.1882
84	6.4123	0.4758	5.6841	7.9309

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.39065	0.01709	0.35716	0.42414
Scale	0.07522	0.01602	0.04954	0.11419

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	2.4955	0.1047	2.2986	2.7094
Standard Deviation	0.4355	0.1040	0.2727	0.6954
Interquartile Range(IQR)	0.5757	0.1326	0.3665	0.9041

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	2.4584	0.09673	2.2860	2.7145
First Quartile(Q1)	2.1873	0.08483	1.9873	2.3530
Third Quartile(Q3)	2.7630	0.1470	2.5430	3.2383

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	2.0694	0.09059	1.8347	2.2285
50	2.4584	0.09673	2.2860	2.7145
84	2.9205	0.1817	2.6597	3.5410

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.4554	0.3940	0.5302

Male Rats, 240 min GF and GB Exposures, 14-Day Deaths

Distribution: Lognormal base 10

Response Information

Variable	Value	Count
Dead 2w	Success	29
	Failure	41
Exposed	Total	70

Factor Information

Factor	Levels	Values
Agent	2	GB GF

Estimation Method: Maximum Likelihood

Regression Table

Variable	Coef	Standard Error	Z	P
Constant	-9.273	1.984	-4.67	0.000
Conc	12.895	2.772	4.65	0.000
Agent				
GF	4.308	1.034	4.17	0.000
Natural Response	0.000			

Test for equal slopes: Chi-Square = 3.7396, DF = 1, P-Value = 0.053
Log-Likelihood = -32.826

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	4.464	3	0.215
Deviance	5.657	3	0.130
Hosmer-Lemeshow	4.464	4	0.347

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	0	4	2	6	8	9	29
Exp	1.3	2.8	2.9	5.7	6.5	9.6	
Failure							
Obs	10	16	8	4	2	1	41
Exp	8.7	17.2	7.1	4.3	3.5	0.4	
Total	10	20	10	10	10	10	70

Agent = GB

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.71914	0.02574	0.66869	0.76959
Scale	0.07755	0.01667	0.05088	0.11819

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	5.3219	0.3215	4.7276	5.9909
Standard Deviation	0.9579	0.2292	0.5994	1.5310
Interquartile Range(IQR)	1.2647	0.2912	0.8054	1.9861

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	5.2377	0.3104	4.6378	5.9940
First Quartile(Q1)	4.6434	0.2878	3.9777	5.2143
Third Quartile(Q3)	5.9081	0.3974	5.2591	7.0846

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	4.3855	0.2931	3.6645	4.9257
50	5.2377	0.3104	4.6378	5.9940
84	6.2555	0.4628	5.5418	7.7253

Agent = GF

Tolerance Distribution

Parameter Estimates

Parameter	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Location	0.38506	0.01704	0.35166	0.41845
Scale	0.07755	0.01667	0.05088	0.11819

Characteristics of Distribution

	Estimate	Standard Error	95.0% Normal CI Lower	Upper
Mean(MTTF)	2.4659	0.1033	2.2716	2.6769
Standard Deviation	0.4439	0.1067	0.2771	0.7111
Interquartile Range(IQR)	0.5860	0.1355	0.3724	0.9221

	Estimate	Standard Error	95.0% Fiducial CI Lower	Upper
Median	2.4269	0.09522	2.2552	2.6767
First Quartile(Q1)	2.1515	0.08541	1.9456	2.3149
Third Quartile(Q3)	2.7376	0.1460	2.5191	3.2117

Table of Percentiles

Percent	Percentile	Standard Error	95.0% Fiducial CI Lower	Upper
16	2.0321	0.09228	1.7887	2.1914
50	2.4269	0.09522	2.2552	2.6767
84	2.8985	0.1817	2.6384	3.5236

Table of Relative Potency

Factor: Agent

Comparison	Relative Potency	95.0% Fiducial CI Lower	Upper
GB VS GF	0.4634	0.4006	0.5421

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APPENDIX B

PROBIT-TYPE BINARY LOGISTIC REGRESSION ANALYSES FOR EFFECTS OF SEX, CONCENTRATION, AND AGENT ON LETHAL RESPONSE TO VAPOR EXPOSURE

Female and Male Rats, 10 min GF and GB Exposures, 24-hr Deaths B-2

Female and Male Rats, 10 min GF and GB Exposures, 14-Day Deaths B-3

Female and Male Rats, 60 min GF and GB Exposures, 24-hr Deaths B-4

Female and Male Rats, 60 min GF and GB Exposures, 14-Day Deaths B-5

Female and Male Rats, 240 min GF and GB Exposures, 24-hr Deaths..... B-6

Female and Male Rats, 240 min GF and GB Exposures, 14-Day Deaths B-7

Female and Male Rats, 10 min GF and GB Exposures, 24-hr Deaths

Binary Logistic Regression: Dead 1d, Exposed versus logC, Agent, Gender

Link Function: Normit

Response Information

Variable	Value	Count
Dead 1d	Success	84
	Failure	146
Exposed	Total	230

Factor Information

Factor	Levels	Values
Agent	2	GB GF
Gender	2	-1 1

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-43.612	7.538	-5.79	0.000
logC	31.819	5.476	5.81	0.000
Agent				
GF	-1.0419	0.2528	-4.12	0.000
Gender				
1	19.063	8.398	2.27	0.023
Gender*logC				
1	-15.476	5.950	-2.60	0.009

Log-Likelihood = -81.949
Test that all slopes are zero: G = 138.028, DF = 4, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	14.725	18	0.681
Deviance	15.326	18	0.639
Hosmer-Lemeshow	3.580	6	0.733

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group								
Value	1	2	3	4	5	6	7	8	Total
Success									
Obs	0	0	3	9	10	19	23	20	84
Exp	0.0	0.2	3.5	5.8	11.1	19.4	24.3	19.6	
Failure									
Obs	30	30	27	21	20	11	7	0	146
Exp	30.0	29.8	26.5	24.2	18.9	10.6	5.7	0.4	
Total	30	30	30	30	30	30	30	20	230

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	10998	89.7%	Somers' D	0.81
Discordant	1008	8.2%	Goodman-Kruskal Gamma	0.83
Ties	258	2.1%	Kendall's Tau-a	0.38
Total	12264	100.0%		

Female and Male Rats, 10 min GF and GB Exposures, 14-Day Deaths

Binary Logistic Regression: Dead 1d, Exposed versus logC, Agent, Gender

Link Function: Normit
Response Information

Variable	Value	Count
Dead 2w	Success	88
	Failure	142
Exposed	Total	230

Factor Information

Factor	Levels	Values
Agent	2	GB GF
Gender	2	-1 1

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-45.063	7.763	-5.80	0.000
logC	32.964	5.646	5.84	0.000
Agent				
GF	-1.2348	0.2616	-4.72	0.000
Gender				
1	19.492	8.489	2.30	0.022
Gender*logC				
1	-15.787	6.032	-2.62	0.009

Log-Likelihood = -80.154
Test that all slopes are zero: G = 145.743, DF = 4, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	19.160	18	0.382
Deviance	20.446	18	0.308
Hosmer-Lemeshow	6.797	6	0.340

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

				Group					
Value	1	2	3	4	5	6	7	8	Total
Success									
Obs	0	0	2	11	10	19	26	20	88
Exp	0.0	0.2	3.7	6.4	11.6	21.0	25.4	19.7	
Failure									
Obs	30	30	28	19	20	11	4	0	142
Exp	30.0	29.8	26.3	23.6	18.4	9.0	4.6	0.3	
Total	30	30	30	30	30	30	30	20	230

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	11333	90.7%	Somers' D	0.83
Discordant	903	7.2%	Goodman-Kruskal Gamma	0.85
Ties	260	2.1%	Kendall's Tau-a	0.40
Total	12496	100.0%		

Female and Male Rats, 60 min GF and GB Exposures, 24-hr Deaths

Binary Logistic Regression: Dead 1d, Exposed versus logC, Agent, Gender

Link Function: Normit

Response Information

Variable	Value	Count
Dead 1d	Success	75
	Failure	65
Exposed	Total	140

Factor Information

Factor	Levels	Values
Agent	2	GB GF
Gender	2	-1 1

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-19.480	3.176	-6.13	0.000
logC	25.113	4.053	6.20	0.000
Agent				
GF	0.8118	0.2916	2.78	0.005
Gender				
1	-1.9786	0.3845	-5.15	0.000

Log-Likelihood = -56.425
Test that all slopes are zero: G = 80.516, DF = 3, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	15.061	12	0.238
Deviance	17.225	12	0.141
Hosmer-Lemeshow	6.476	6	0.372

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group								
Value	1	2	3	4	5	6	7	8	Total
Success									
Obs	1	2	5	10	6	16	15	20	75
Exp	0.5	1.9	4.7	10.0	9.7	15.7	13.8	19.6	
Failure									
Obs	19	13	10	10	9	4	0	0	65
Exp	19.5	13.1	10.3	10.0	5.3	4.3	1.2	0.4	
Total	20	15	15	20	15	20	15	20	140

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	4282	87.8%	Somers' D	0.79
Discordant	442	9.1%	Goodman-Kruskal Gamma	0.81
Ties	151	3.1%	Kendall's Tau-a	0.39
Total	4875	100.0%		

Female and Male Rats, 60 min GF and GB Exposures, 14-Day Deaths

Binary Logistic Regression: Dead 2w, Exposed versus logC, Agent, Gender

Link Function: Normit

Response Information

Variable	Value	Count
Dead 2w	Success	77
	Failure	63
Exposed	Total	140

Factor Information

Factor	Levels	Values
Agent	2	GB GF
Gender	2	-1 1

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-18.047	2.986	-6.04	0.000
logC	23.454	3.817	6.14	0.000
Agent				
GF	0.7422	0.2883	2.57	0.010
Gender				
1	-1.9864	0.3772	-5.27	0.000

Log-Likelihood = -58.018
Test that all slopes are zero: G = 76.643, DF = 3, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	17.739	12	0.124
Deviance	19.444	12	0.078
Hosmer-Lemeshow	7.357	6	0.289

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group								
Value	1	2	3	4	5	6	7	8	Total
Success									
Obs	1	3	5	11	6	16	15	20	77
Exp	0.6	2.4	5.0	10.6	10.1	15.7	13.9	19.5	
Failure									
Obs	19	12	10	9	9	4	0	0	63
Exp	19.4	12.6	10.0	9.4	4.9	4.3	1.1	0.5	
Total	20	15	15	20	15	20	15	20	140

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	4219	87.0%	Somers' D	0.77
Discordant	479	9.9%	Goodman-Kruskal Gamma	0.80
Ties	153	3.2%	Kendall's Tau-a	0.38
Total	4851	100.0%		

Female and Male Rats, 240 min GF and GB Exposures, 24-hr Deaths

Binary Logistic Regression: Dead 2w, Exposed versus logC, Agent, Gender

Link Function: Normit

Response Variable	Information Value	Count
Dead 1d	Success	59
	Failure	71
Exposed	Total	130

Factor Information

Factor	Levels	Values
Gender	2	-1 1
Agent	2	GB GF

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-12.377	2.204	-5.61	0.000
logC	22.744	4.177	5.45	0.000
Gender				
1	2.680	1.074	2.49	0.013
Agent				
GF	4.5210	0.8540	5.29	0.000
Gender*logC				
1	-9.499	2.750	-3.45	0.001

Log-Likelihood = -57.538
Test that all slopes are zero: G = 64.034, DF = 4, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	6.092	6	0.413
Deviance	6.888	6	0.331
Hosmer-Lemeshow	1.886	4	0.757

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	3	2	9	11	15	19	59
Exp	3.3	3.1	7.3	10.4	14.7	19.5	
Failure							
Obs	27	18	11	9	5	1	71
Exp	26.7	16.9	12.7	9.6	5.3	0.5	
Total	30	20	20	20	20	20	130

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	3530	84.3%	Somers' D	0.74
Discordant	440	10.5%	Goodman-Kruskal Gamma	0.78
Ties	219	5.2%	Kendall's Tau-a	0.37
Total	4189	100.0%		

Female and Male Rats, 240 min GF and GB Exposures, 14-Day Deaths

Binary Logistic Regression: Dead 2w, Exposed versus logC, Agent, Gender

Link Function: Normit

Response Variable	Information Value	Count
Dead 2w	Success	63
	Failure	67
Exposed	Total	130

Factor Information

Factor	Levels	Values
Gender	2	-1 1
Agent	2	GB GF

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-10.787	2.075	-5.20	0.000
logC	19.773	3.948	5.01	0.000
Gender				
1	1.877	1.021	1.84	0.066
Agent				
GF	4.1120	0.8136	5.05	0.000
Gender*logC				
1	-7.364	2.623	-2.81	0.005

Log-Likelihood = -61.805
Test that all slopes are zero: G = 56.485, DF = 4, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	6.133	6	0.408
Deviance	7.512	6	0.276
Hosmer-Lemeshow	3.079	4	0.545

Table of Observed and Expected Frequencies:
(See Hosmer-Lemeshow Test for the Pearson Chi-Square Statistic)

	Group						
Value	1	2	3	4	5	6	Total
Success							
Obs	4	4	7	13	16	19	63
Exp	2.9	6.2	7.8	10.9	15.3	19.5	
Failure							
Obs	16	26	13	7	4	1	67
Exp	17.1	23.8	12.2	9.1	4.7	0.5	
Total	20	30	20	20	20	20	130

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	3443	81.6%	Somers' D	0.69
Discordant	523	12.4%	Goodman-Kruskal Gamma	0.74
Ties	255	6.0%	Kendall's Tau-a	0.35
Total	4221	100.0%		